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Development and characterization of a scalable microperforated device capable of long-term zero order drug release

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Abstract A drug delivery system that consists of microperforated polyimide microtubes was developed and characterized. Two groups of polyimide tubes were used. One set consisted of microtubes (I.D.=125 μm) with 32.9±1.7 μm size holes. The second set consisted of larger tubes (I.D.=1000 μm) with 362–542 μm holes. The number of holes was varied between 1 and 3. The small tubes were loaded with crystal violet (CV) and ethinyl estradiol (EE) and the drug release studies were performed in 0.01 M phosphate buffered saline (PBS) (pH 7.1–7.4) at 37.0±1.0°C for upto 4 weeks. The large tubes were loaded with CV and the drug release was studied *in vitro* in PBS and also *ex vivo* in rabbit's vitreous humor. Linear release rates with R^2>0.9900 were obtained for all groups with CV and EE. Release rates of 7.8±2.5, 16.2±5.5, and 22.5±6.0 ng/day for CV and 30.1±5.8 ng/day for EE were obtained for small tubes. For large tubes, a release rate of 10.8±4.1, 15.8±4.8 and 22.1±6.7 μg/day was observed *in vitro* in PBS and a release rate of 5.8±1.8 μg/day was observed *ex vivo* in vitreous humor.

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1 Introduction

Long term drug therapy is desirable for patients suffering with chronic conditions such as chronic pain, vitroretinal diseases, and diabetes. Chronic pain is experienced by those who are seriously injured or burned, and may require amputation of limbs (Black and McManus 2009). Vitroretinal diseases affect the posterior segment of the eye and include posterior uveitis, age-related macular degeneration, and macular edema (Hsu 2007).

Long term drug therapy may be performed from months to years and include multiple dosing with incremental increase in the dose (Markman and Philip 2007). In such a scenario, a health provider's concern is compounded by the fact that a high dose regimen may initiate other complications and side effects (Berde and Nurko 2008; Kempen et al. 2008). A need for frequent systemic dosing may also result in patient distress and interfere with their day to day activities.

In addition, continuously delivering drugs across the natural physiological barriers such as the blood-eye barrier or the blood-cerebrospinal fluid may be challenging using conventional dosage forms (Edward et al. 1999; Urtti 2006). A suitable alternate, to overcome these problems, would be to utilize a drug delivery system that is capable of locally delivering constant amounts of drugs (zero-order release) for prolonged periods.

Diffusion controlled reservoir type devices are known to yield zero order release rates due to the concentration gradient maintained across the membrane (Swarbrick and Boylan 2002). Common examples of such devices that are capable of long term zero order release are the contracep-

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tive implant, Norplant, and the ocular implant, Ocusert (Macoul and Pavan-Langston 1975; Segal 1983; Shi 2004). However, in these devices membrane effects may become rate controlling steps and phenomena such as 'boundary layer problem', 'burst effect', and 'membrane rupture' have been described (Robinson and Lee 1987). A boundary layer problem arises when drug release is stalled due to drug saturation at the membrane (Zhou and Wu 2003). A burst effect may be observed when a device, which is stored for a long time, exhibits rapid release due to prior accumulation of drug at the membrane (Robinson and Lee 1987). A similar occurrence is also seen with polymer controlled drug delivery systems (Huang and Brazel 2001). Membrane rupture may result in drug dumping causing toxicity concerns (Ratner et al. 2004).

The present investigation presents a potential solution to these problems. Data obtained from the development and evaluation of an impermeable microtube with micro perforations on one side of the surface of the tube is presented demonstrating long term zero order drug release from the device. This delivery system is applicable to a variety of disease states ranging from cancer to pain management. Drug release from the device is dependent on the solubility of the drug, the distance between the holes, and the area available for drug diffusion. The diffusion area in turn is dependent on the number of holes and the size of the holes. Since, the size of the holes is very small as compared to the total device size and the distance between the holes, the release rate from each hole is independent from each other as long as the basic conditions of solubility and sink conditions are met.

A series of experiments were designed to determine the release rates from the perforated microtubes. Different sized microtubes were used to study the effect of device size. The number of holes and size of the holes were varied to study their effect on drug release. For groups containing one hole, the hole was centrally made on one side of the tube's surface. For more than one hole; the holes were fabricated symmetrically and equidistant from each other and also from the ends of the tubes. The holes were fabricated using laser drilling and/or photolithography techniques. However, holes on the large tubes were made using mechanical micro drilling. In all cases, only the exposed surface of the tube was perforated and the underlying surface remained intact.

In the study, crystal violet (CV), (N-[4-[Bis[4-(dimethylamino)phenyl]methylene]-2,5-cyclohexadien-1-ylidene]-N-methylmethanaminium chloride) (Merck-Index 2006), was selected as the model drug and the perforated device was manufactured using polyimide matrices. The capability of the device as a zero order drug delivery system was further tested using a second drug (ethinyl estradiol, EE) and also by performing the release studies in a biological fluid (rabbit's vitreous humor).

2 Materials and methods

2.1 Materials

Polyimide tubes were obtained from Microlumen Inc. (Tampa, FL, USA). Crystal violet was obtained from Sigma-Aldrich (St. Louis, MO, USA). Ethinyl estradiol was obtained from Sigma-Aldrich (St. Louis, MO, USA). Rabbit's vitreous humor was obtained from Pel-Freez Biologicals (Rogers, AR, USA). Sodium azide was obtained from Mallinckrodt (Hazelwood, MO, USA). Ethinyl estradiol ELISA kit was purchased from Abraxis Kits (Warminster, PA, USA). Bioglue™, a biocompatible glue was obtained from Cryolife (Kennesaw, GA, USA). Heat shrink polyolefin tubing (3.0 mm diameter) was obtained from Altex (San Antonio, TX, USA). Microvials (0.3 ml) were obtained from Perkin-Elmer (Waltham, MA, USA). Glass vials (2.0 ml) were obtained from Agilent (Santa Clara, CA, USA). Drill bits of different sizes (Dremel®, Racine, WI, USA) were obtained from Hobby Town (San Antonio, TX, USA).

2.2 Fabrication of holes and drug loading

2.2.1 Small tubes

Polyimide tubes (I.D.=125 μm, referred to in text as small tubes) were cut to 20 mm in length. Three subsets of perforated polyimide tubes having a one hole, two holes, or three holes through the tube's surface were prepared (Fig. 1). The holes can be produced by either laser drilling or photolithography techniques (Linder et al. 1996; Li et al. 2001; Stover et al. 2007). Initially laser drilling was used to fabricate the microholes on the microtubes, however a more

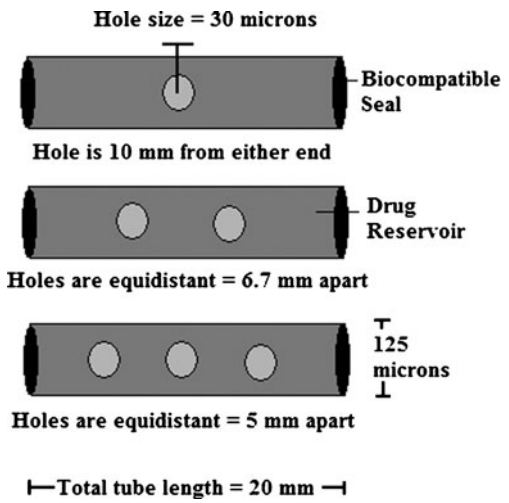

Fig. 1 Polyimide tubes with different number of holes on the surface. The holes are equidistant from each other and also from the ends of the tube

economical and practical method amenable to mass production was developed using photolithographic techniques. Figure 2 shows examples of micro holes fabricated using laser and photolithography techniques. The lithography process which has been used to fabricate holes has been covered in our United States Provisional Patent Application (61/225,309 and 61/225,352). The technology to fabricate micro-structures on planar silicon wafers is well developed. The patents define the methods which can be used to fabricate micro-structures such as micro holes on non planar surfaces, for example, polyimide tubes.

Loading of these microtubes was achieved using a highly concentrated solution of CV in ethanol (400 mg/ml), prepared by heating to 80°C. Drug loading of the solution inside the perforated tubes was achieved using capillary action. The tubes were allowed to stand overnight at room temperature to evaporate the alcohol. The ends of the tubes were plugged with a stainless steel wire (120 μm diameter) (Small Parts Inc., Miramar, FL, USA) and sealed with biocompatible glue.

After the release studies with CV, the set of small tubes with three equidistant holes were washed and dried. As with CV, the tubes were reloaded with a high concentrated solution of EE in alcohol (160 mg/ml) and ends plugged using the stainless steel wire.

2.2.2 Large tubes

A larger polyimide tubes (I.D.=1000 μm, referred to in text as large tubes) for releasing larger amounts of CV were used. The holes were manually drilled using drill bits on one surface of the tube without penetrating through the other surface. Three subsets were prepared differing from each other in either number of holes or size of the holes. For the first subset, 10 mm tubes were cut in length and a single hole was fabricated at the center using a drill bit; the second subset had two holes on 15 mm tubes (placed at 5 mm from each other and also from the ends); and the third subset consisted of one larger size hole centrally drilled on 10 mm tubes. Appropriate sized drill bits were used to yield approximately 360 μm diameter and 540 μm diameter holes for first two subsets and the third subset, respectively. The tubes were manually and tightly packed with CV powder. Heat shrink polyolefin tubes were used to cap the ends of the tubes. The heat shrink tubes were placed at the end of the CV loaded tubes and heat was applied. The polyolefin tubes shrank due to heat and were immediately crimped to ensure proper sealing of the CV loaded tubes. The first subset tubes were also re-used for drug release studies in vitreous humor.

2.3 *In vitro* drug release studies

2.3.1 Small tubes

The CV loaded tubes were placed in microvials containing 0.3 ml of PBS (0.01 M phosphate, pH 7.4). A blank polyimide tube was used as an experimental control. The vials were placed on a drug dissolution apparatus having a dip rate of 30–32 dips/min. The apparatus was connected to a water bath maintained at 37.0±1.0°C, for the duration of study. The method was developed in accordance to the method proposed by Varian Inc for *in vitro* testing of drug delivery devices (Varian-Inc. 2009). Aliquots were withdrawn every 2 days and replenished with fresh buffer. The collected samples were analyzed spectrophotometrically at 590 nm to estimate the amount of CV released.

A similar but simpler dissolution method was developed for EE loaded tubes and subsequent studies. The microvials were placed on a rocker (46-48 oscillations/min), instead of dissolution apparatus, and maintained inside an incubator (37.0±1.0°C) for the entire duration of study. The aliquots were collected at regular intervals and quantitatively estimated for EE using the ethinyl estradiol ELISA Kit, according to the manufacturer's protocol. Briefly, samples were diluted using 10% (v/v) methanol. The antigen-enzyme conjugate powder was reconstituted with 7 ml of buffer solution. A 100 μl of EE2 standards (or sample) was

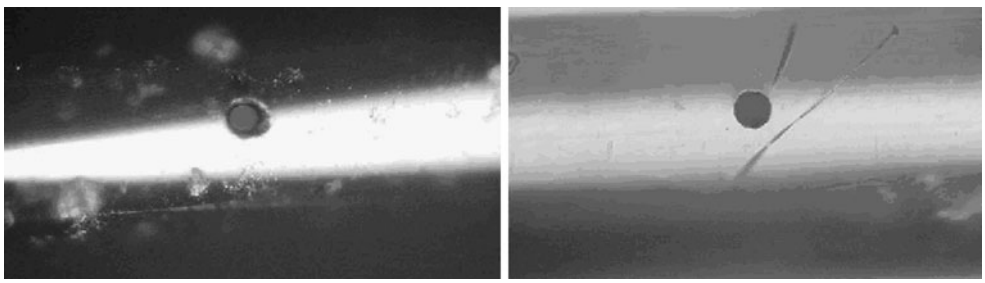

Fig. 2 Holes drilled using laser (left; magnification=20X; Tube I.D.=125.0 μm; Hole diameter=32.9±1.7 μm; n=45) and photolithography (right; magnification=20X; Tube I.D.=125.0 μm; Hole diameter=20.0±1.1 μm; n=27) on the surface of polyimide tubes. The drilling/etching process was restricted to one surface of the tube such that the underlying surface remained unetched

mixed with a 100 μl of conjugate solution and 100 μl of the mixture was added to the coated microplate included in the kit. After sufficient incubation time, a 100 μl of color solution was added followed by addition of 100 μl of stop solution after 30 min. The standard and sample absorbance was measured using a spectrophotometer at 450 nm. The standard curve was constructed utilizing a four-parameter logistic curve fitting program. The concentration of EE in the unknowns was determined by interpolation. Duplicate assays were performed for each standard and sample.

2.3.2 Large tubes

Rabbit's vitreous humor was prepared for the kinetic studies according to the previously published study (Steffansen et al. 1996). Briefly, the vitreous humor was centrifuged at 1900 rpm for 2 min and the supernatant was collected and diluted with PBS (0.01 M, pH 7.1) to provide a 1:1 v/v dilution. A 0.05%w/v sodium azide was added as a preservative. The CV loaded tubes were transferred to glass vials containing 1.5 ml of PBS (0.01 M phosphate, pH 7.1) and 1.0 ml of diluted vitreous humor. As with the small tubes, the glass vials were put on the rocker and maintained inside the incubator (37.0±1.0° C). Empty polyimide tubes and CV loaded non-perforated polyimide tubes with heat shrink caps were used as experimental controls. Samples were withdrawn at regular intervals and assayed as for the small tubes.

2.4 Statistical analysis

Levene's test was used to access the homogeneity of variance in various groups. One way ANOVA with post hoc analysis using Tukey-HSD test (equal variance assumed) or Games Howell test (equal variances not assumed) through SPSS statistical software was used to analyze difference amongst the subsets with respect to hole size and drug loading. Linear regression analysis was performed on the cumulative release data and F-statistics was used to estimate the association between the amount of release and time points. A difference of p value<0.05 was considered significant.

3 Results

3.1 Small tubes

The diameter of the holes was measured as 32.9± 1.7 μm. Micro-gravimetric analysis yielded an average of 127.1±11.9 and 57.9±9.7 μg of CV and EE loaded in the tubes, respectively. A statistical significant difference was not observed amongst the three groups with respect to hole size or drug loading, $p>0.05$. A supersaturated solution of CV was used to load the tubes. However, other techniques such as the ones used for filling HPLC columns with stationary phases might also be used to fill the microtubes.

Crystal violet released from the microtubes was monitored *in vitro* for 28 days (Fig. 3). The three subsets differed only in the number of holes on the surface, namely one hole, two holes, and three holes. The release of CV was found to be linear with R^2 values of 0.9945, 0.9998, and 0.9998 for the three subsets. The F-statistics, F(1,28), $p<0.05$, revealed a close association between the amount of drug released and time that strengthened the observed linearity in release. The average amount of CV released was 7.8±2.5, 16.2±5.5, and 22.5±6.0 ng/day for one hole, two holes, and three holes, respectively. The data suggests a linear relationship between drug release and number of holes. As illustrated in Fig. 4, the release rate increased linearly with increasing numbers of holes.

The linearity of release was further tested by performing kinetic studies with EE in PBS. The aliquots derived from the study were analyzed using ELISA. Zero order drug release profile with R^2 value of 0.9996 was obtained with the drug release rate of 30.1±5.8 ng/day (Fig. 5). The linearity of the release was further confirmed by F test, F (1, 12) and F (1, 12), $p<0.05$.

These results suggest that in a multiple hole setting the release of drug from one hole is independent of the other. Assuming a constant rate of release from each hole, the amount of drug released when correlated to the total amount of drug loaded, suggests a total duration of release of more than 3 years.

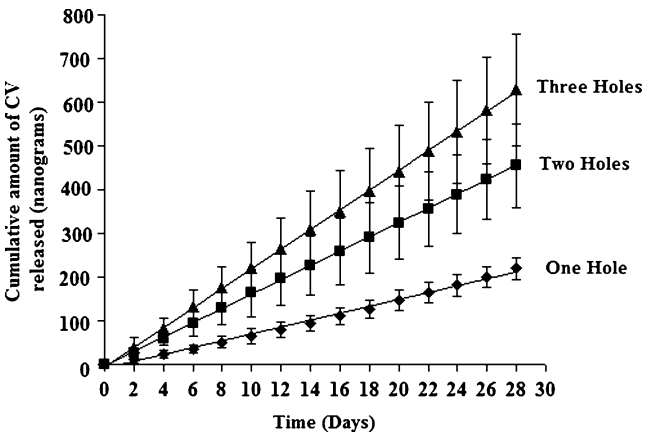

Fig. 3 A constant amount of crystal violet was released from the three subsets. The solid lines represent the regression lines. The slopes of the lines are the rate of drug release per day. The data is represented as mean with standard deviation, $n=7$

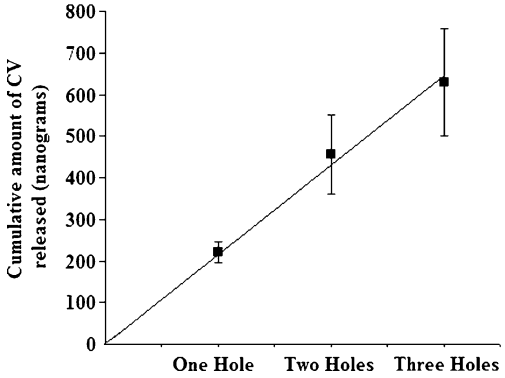

Fig. 4 Comparison of cumulative amount of CV released from the three groups of small tubes after 28 days. A linear relationship between release rate and number of holes was observed. The drug release increase additively with increase in number of holes. The cumulative amount of CV release after 28 days is 220.1±25.0, 455.7± 95.6, and 628.9±128.2 ng for one hole, two holes, and three holes group. The data is represented as mean with standard deviation

3.2 Large tubes

Three subsets of large holes were prepared: The first subset consisted of one hole (365.3±16.7 μm); the second subset consisted of two holes (362.4±23.1 μm); and the third subset consisted of one larger size hole (542.6±26.3 μm). The 365 μm hole tubes were used for kinetic studies in buffer as well as in vitreous humor. The coefficient of variation for hole size measurement for each of the three groups was less than five percent. The gravimetric analysis yielded the average amount of CV loaded per unit length in the groups as 5.3±0.3, 5.2±0.3, and 5.4±0.2 mg/cm, respectively. Statistical analysis for drug loading did not yield any significant difference amongst the groups, $p>0.05$.

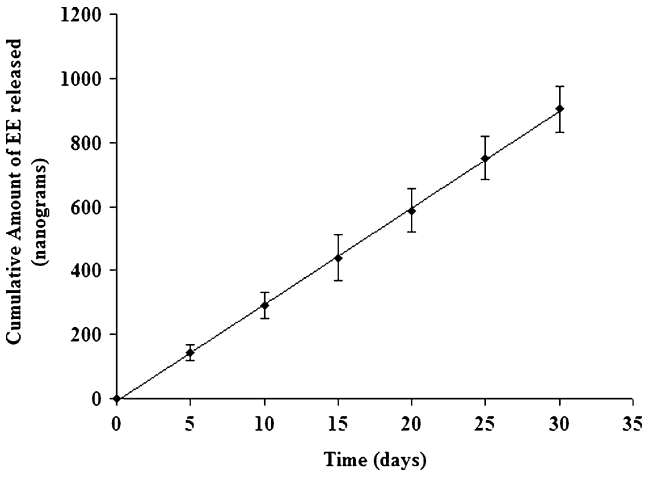

Fig. 5 Cumulative amount of EE released from 30 micron group over 30 days. The release profile exhibits a zero order kinetics with R^2= 0.9996. The slope of the line indicates the rate of EE release of 30.1± 5.8 ng/day. The data is represented as mean with standard deviation, n=7

The rate of CV release from loaded tubes was found to be linear in phosphate buffered saline (Fig. 6). The R^2 was found to be 0.9958, 0.9947, and 0.9979 for the 365.3 (one hole), 362.1 (two holes), and 542.6 (one big hole) μm holes respectively. The linearity of the release was further confirmed by F test, F (1, 56), $p<0.05$. The average amount of 10.8±4.1, 15.8±4.8 and 22.1±6.7 μg/day of CV was released from the three sets.

The efficacy of the device was tested by performing the CV release studies in the rabbit's vitreous humor. The R^2 was found to be 0.9909 with a drug release rate of 5.8±1.8 μg/ day (Fig. 7). The F test, F (1, 14), $p<0.05$ further established the capability of the drug delivery system for a long term zero order release. The release data yet again suggest a linear relationship between number of holes and drug release. The release data also suggests the total duration of release of approximately 1 year or longer from the three groups.

4 Discussion

A drug delivery system has been developed which may lead to efficient management of a chronic diseased state by delivering therapeutic amounts of drug locally at a constant rate to the target site. A local zero order release of drug would ensure maximum benefits with minimum side effects. Only a lower dose of drug at the target site will be needed as opposed to higher doses required by other routes of administration.

In the study, perforated tubes of different sizes were used to evaluate the scalability of the device. Polyimide was used because it is biocompatible, chemically inert, and widely used in fabrication of implantable micro electrodes and capable of holding microelectronic components (Niwa et al. 2001; Geddes and Roeder 2003; Kawakami et al. 2003). We have developed in-house methods to fabricate

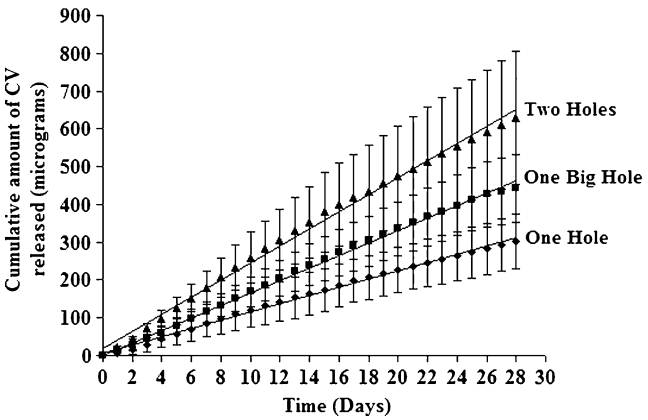

Fig. 6 Cumulative release profile of CV from the three subsets. The solid lines represent the regression lines of the three subsets. The data is represented as mean with standard deviation, n=12

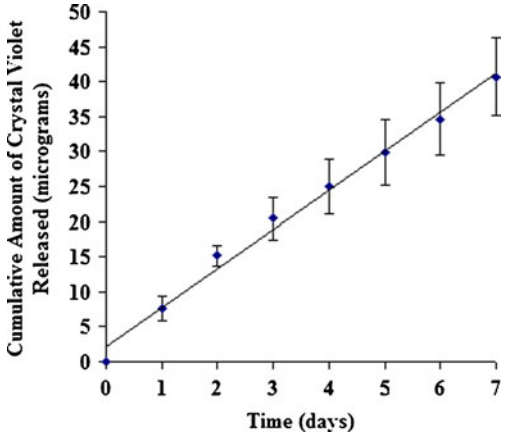

Fig. 7 A linear release of crystal violet was observed ex vivo in rabbit's vitreous humor with R^2=0.9909. The solid line represents the regression line. The slope of the line indicates the rate of drug release. Data is presented as mean with standard deviation, n=7

micro holes on the microtubes. Based on our experience lithographic techniques should be more cost effective for mass production of the device. However, lithography and laser drilling can be complex for someone not familiar with the techniques and can opt for commercially available vendors who have capability to laser drill micro holes on various substrates. It is also our experience that for experimental purposes drill bits can be used to fabricate holes greater than 300 μm in diameter.

The drug release from both small tubes and large tubes yielded zero order release. We observed that the agitation with rocker is greater than with the dissolution apparatus which may cause variability in release rate between the two methods.

Ethinyl estradiol (EE) is a common contraceptive similar to levonorgesterol, which is the active ingredient of the reservoir type device, Norplant (Shaaban et al. 1984). EE was used because similar to crystal violet it is also soluble in alcohol, which assisted in the drug loading of small tubes. The triphenylmethane dye, crystal violet was selected as the model drug because of its physical properties. It is a commonly used biological staining agent with anti-fungal properties (Bragulat et al. 1991) and high molar extinction coefficient, making it easily detectable spectrophotometrically even at very low concentrations (Safarik and Safarikova 2002; Safarikova and Safarik 2002). However, EE does not have a similar advantage of high molar extinction coefficient and hence a bioassay was utilized to quantitatively measure its amount in the drug release samples. ELISA test is based on the competitive reaction where EE competes with the antigen-enzyme conjugate for a limited number of binding sites of specific antibodies immobilized on the surface of the wells (AbraxisKits 2009).

Although, a zero order release rate was observed for crystal violet in rabbit's vitreous humor, the release was slower than in buffer. The greater viscosity of vitreous humor due to presence of hyaluronic acid and collagen may have resulted in slower release profiles (Reddy and Kinsey 1960). Other factors such as drug-protein interaction are also known to influence the rate of drug release (Boubriak et al. 2000).

4.1 Mechanism of release kinetics

The drug release from the device can be explained by drug dissolution due to surface erosion of the drug at the hole/drug solvent interface. The impermeable tube protects the enclosed drug and the hole allows for exposure of small amounts of drug inside the tube. The exposed drug layer is solubilised by the solvent and the solution diffuses out. Drug release is controlled by various factors such as, surface area of the drug that is exposed, solubility of the drug, drug loading, and drug packing. The exposed surface area is dependent on the number of holes and size of the holes on the surface.

Mathematical model- The Noyes Whitney's equation for dissolution is given by:

$$\frac{dM}{dT} = \frac{D}{L} \bullet (Cs - C) \bullet A \tag{1}$$

where, $\frac{dM}{dT}$, D, L, Cs, C, and A are rate of drug dissolution, diffusion coefficient of the drug, diffusion layer thickness, solubility of the drug, concentration of the drug in dissolution medium, and area available for dissolution.

For a perforated device, with 'n' number of microholes; A will be the area of each hole. In addition, the concentration of the drug inside the device is greater than in the medium rendering sink conditions, C<<Cs. Thus, for a perforated device loaded with drug, Eq. (1) is reduced to

$$\frac{dM}{dT} = \frac{D}{L} \bullet Cs \bullet A \bullet n \tag{2}$$

Apparent permeability coefficient- The apparent permeability coefficients (D/L) of CV, with respect to the perforated device can be calculated from Eq. (2). For one hole (365.3 ±16.7 μm) and one larger sized hole (542.6±26.3 μm) subsets in large tubes, D/L values were calculated as 6.08×10^{-5} cm/sec and 4.01×10^{-5} cm/sec, respectively. For the one hole group in small tubes (32.9±1.7 μm), the D/L was calculated as 5.7×10^{-6} cm/sec. The difference in D/L values obtained from large tubes and small tubes may be attributed to the difference in ratio of hole size with respect to the device size in two groups. A greater ratio will lead to faster diffusion and vice versa as also suggested by the D/L values. For a multi-hole setting, it is our observation that the hole diameter should be comparatively smaller than the

device diameter and also to the distance between the adjacent holes. This is imperative for drug to be released independently from each hole, which may lead to additive effect as seen in Fig. 4.

Desired drug release rates- The drug delivery system can be used for a variety of disease conditions by varying the realease rates. A desired rate of drug release from the device can be calculated using Eq. 2. Previously calculated D/L, solubility of the drug, area of the hole can be utilized and the number of holes (n) on the device can be manipulated to yield the rate of drug release desired from the device.

5 Conclusion

A novel microperforated drug delivery platform capable of delivering drugs was devised and evaluated *in vitro* and *ex vivo*. The capability of the delivery system to produce zero order kinetics in different dimensions, with different drugs, and in different dissolution mediums indicates its versatility, scalability, and effectiveness for long term zero order release. The *in vitro* release rates were found to be proportional to the exposed surface area of the drug. They were linear as a function of number of holes. Drug release from the device depends on the drug's solubility, drug loading, drug packing, number of holes, and hole size. The concentration gradient across the hole is the main driving force for release of drug from the device. The rate and extent of drug release may be tailored by manipulating the size of the reservoir, number of holes, hole size, and drug solubility. The equidistant holes acted independently and the drug release from each hole was independent of the other. It should be possible to use such a device for local and controlled delivery of drugs; as a protective carrier to transport labile drugs; and as an implant for treatment of various chronic conditions.

References

AbraxisKits. http://www.abraxiskits.com/moreinfo/PN590051USER.pdf Accessed on Jun 05 2009

C. Berde, S. Nurko, N. Engl. J. Med. **358**(22), 2400–2402 (2008)

I.H. Black, J. McManus, Prehosp. Emerg. Care **13**(2), 223–227 (2009)

O.A. Boubriak, J.P. Urban, S. Akhtar, K.M. Meek, A.J. Bron, Exp. Eye Res. **71**(5), 503–514 (2000)

M.R. Bragulat, M.L. Abarca, M.T. Bruguera, F.J. Cabanes, Appl. Environ. Microbiol. **57**(9), 2777–2780 (1991)

A.N. Edward, N.J. Abbott, L. Drewes, Q.R. Smith, P. Couraud, E.A. Chiocca, K.L. Audus, N.H. Greig, N.D. Doolittle, Neurosurgery **44**(3), 604–608 (1999)

L.A. Geddes, R. Roeder, Ann. Biomed. Eng. **31**(7), 879–890 (2003)

J. Hsu, Curr. Opin. Ophthalmol. **18**(3), 235–239 (2007)

X. Huang, C.S. Brazel, J. Control Release **73**(2–3), 121–136 (2001)

H. Kawakami, T. Kanamori, S. Kubota, J. Artif. Organs **6**(2), 124–129 (2003)

J.H. Kempen, S. Gangaputra, E. Daniel, G.A. Levy-Clarke, R.B. Nussenblatt, J.T. Rosenbaum, E.B. Suhler, J.E. Thorne, C.S. Foster, D.A. Jabs, K.J. Helzlsouer, Am. J. Ophthalmol. **146**(6), 802–812 e801 (2008)

Y. Li, K. Itoh, W. Watanabe, K. Yamada, D. Kuroda, J. Nishii, Y. Jiang, Opt. Lett. **26**(23), 1912–1914 (2001)

S. Linder, H. Baltes, F. Gnaedinger, E. Doering, in *Proceedings of IEEE The Ninth Annual International Workshop on Micro Electro Mechanical Systems* (San Diego, CA, USA, 1996), pp. 38–43

K.L. Macoul, D. Pavan-Langston, Arch. Ophthalmol. **93**(8), 587–590 (1975)

J.D. Markman, A. Philip, Anesthesiol. Clin. **25**(4), 883–898 (2007). viii

Merck-Index, *The Merck Index. White House Station, New Jersey*, (Merck & Co., Inc., White House Station, New Jersey, 2006)

M. Niwa, H. Kawakami, M. Kanno, S. Nagaoka, T. Kanamori, T. Shinbo, S. Kubota, J. Biomater. Sci. Polym. Ed. **12**(5), 533–542 (2001)

B.D. Ratner, A.S. Hoffman, F.J. Schoen, J.E. Lemons, *Biomaterial Science: An Introduction to Materials in Medicine London* (Elsivier Academic, London, 2004)

D.V. Reddy, V.E. Kinsey, Arch. Ophthalmol. **63**, 715–720 (1960)

J.R. Robinson, V.H.L. Lee, *Controlled Drug Delivery. Fundamentals and Applications. New York* (Marcel Dekker, New York, 1987)

I. Safarik, M. Safarikova, Water Res. **36**(1), 196–200 (2002)

M. Safarikova, I. Safarik, Eur. Cells Mater. **3**(Suppl 2), 192–195 (2002)

S.J. Segal, Stud. Fam. Plann. **14**(6–7), 159–163 (1983)

M.M. Shaaban, S.I. Elwan, M.Y. el-Kabsh, S.A. Farghaly, N. Thabet, Contraception **30**(5), 421–430 (1984)

D. Shi, *Biomedical devices and their applications New York* (Springer, New York, 2004)

B. Steffansen, P. Ashton, A. Buur, Int. J. Pharm. **132**, 243–250 (1996)

T. Stover, G. Paasche, T. Lenarz, T. Ripken, P. Breitenfeld, H. Lubatschowski, T. Fabian, Cochlear Implants Int. **8**(1), 38–52 (2007)

J. Swarbrick, J.C. Boylan, *Encyclopedia of Pharmaceutical Technology. New York* (Marcel Dekker, New York, 2002)

A. Urtti, Adv. Drug Deliv. Rev. **58**(11), 1131–1135 (2006)

Varian-Inc. http://www.varianinc.com/cgi-bin/nav?products/dissolution/testers/varian400 ds&cid=KNHMOHJMFL Accessed on July 27 2009

Y. Zhou, X.Y. Wu, J. Control Release **90**(1), 23–36 (2003)